



Powles, T. et al. (2016) A randomized, double-blind phase II study evaluating cediranib versus cediranib and saracatinib in patients with relapsed metastatic clear-cell renal cancer (COSAK). *Annals of Oncology*, 27(5), pp. 880-886. (doi:[10.1093/annonc/mdw014](https://doi.org/10.1093/annonc/mdw014))

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/120061/>

Deposited on: 20 July 2016

Article type: Original article

Title: A randomised, double-blind phase II study evaluating cediranib vs cediranib and saracatinib in patients with relapsed metastatic clear cell renal cancer (COSAK).

Author list: T. Powles^{1,7*}, J. Brown², J. Larkin³, R. Jones⁴, C. Ralph², R. Hawkins⁵, S. Chowdhury⁶, E. Boleti¹, A. Bhal⁸, K. Fife⁹, A. Webb¹⁰, S. Crabb¹¹, T. Geldart¹², R. Hill¹³, J. Dunlop¹³, P. E. Hall⁷, D. McLaren¹⁴, C. Ackerman⁷, L. Beltran⁷, P. Nathan¹⁵.

¹The Royal Free NHS Foundation Trust, London, UK.

²University of Sheffield, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

³The Royal Marsden Hospital, London, UK.

⁴The Beatson Cancer Centre, University of Glasgow, Glasgow, UK.

⁵The Christie Hospital, Manchester, UK.

⁶Guys and St Thomas' NHS Foundation Trust, London, UK.

⁷Barts Cancer Institute, CRUK Experiment Cancer Medicine Centre, London, UK.

⁸University Hospital Bristol NHS Foundation trust, Bristol, UK.

⁹Addenbrooke's Cancer Centre, University of Cambridge, Cambridge, UK.

¹⁰West Sussex Cancer Centre, Brighton, UK.

¹¹Southampton NHS Foundation Trust, Southampton, UK.

¹²Royal Bournemouth Hospital, Bournemouth, UK.

¹³Scottish Clinical Trials Research Unit (SCTRU), Partners in CaCTUS, Edinburgh, UK.

¹⁴Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK.

¹⁵Mount Vernon Cancer Centre, Northwood, UK.

***Corresponding Author:**

Professor Thomas Powles

Renal Cancer Lead for London Cancer

Department of Oncology

Royal Free London NHS Foundation Trust

London NW3 2QG, UK

Tel: +44 (0)20 77940500 extension 33667 or direct line +44 (0)20 7472 6778

Fax: +44 (0)20 7794 3341

Email: thomas.powles@bartshealth.nhs.uk

KEY WORDS: Renal cell carcinoma; tyrosine kinase inhibitor; biomarker; SRC; VEGF.

ABSTRACT

BACKGROUND: Preclinical work suggests Src proteins have a role in the development of resistance to vascular endothelial growth factor (VEGF) targeted therapy in metastatic clear cell renal cancer (mRCC)

OBJECTIVE: To test the hypothesis that the addition of a Src tyrosine kinase inhibitor (TKI) saracatinib to VEGF targeted therapy (cediranib) improves outcomes in VEGF resistant mRCC.

DESIGN, SETTING, AND PARTICIPANTS: Patients with disease progression after ≥ 1 VEGF targeted therapy were eligible to participate in this investigator-led, double-blind, randomised (1:1) phase II study. Between 2010 and 2012, 138 patients were randomised across 16 UK sites. Archived tissue was used for biomarker analysis (SRC, FAK, VHL, PTB1b and HIF2 α : n=86).

INTERVENTION: Patients received cediranib 30mg once daily (OD) and saracatinib 175mg OD (CS) (n=69) or cediranib 45mg OD and placebo OD (C) (n=69).

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: The primary endpoint was progression free survival (PFS) by RECIST v1.1 (Response Evaluation Criteria in Solid Tumours v1.1). Secondary endpoints included tolerability, response rates, overall survival (OS). Biomarker analysis was performed.

RESULTS AND LIMITATIONS: The characteristics of the two groups were well balanced. Partial responses were seen in 13.0% for C and 14.5% for CS respectively ($P > 0.05$). There was no significant difference in PFS [5.4 months (3.6-7.3 months) for C and 3.9 (2.4-5.3 months) for CS; Hazard Ratio (HR) 1.18 (0.94-1.48)], or overall survival (OS) [14.2 months (11.2-16.8 months) for C and 10.0 (6.7-13.2 months) for CS; [HR 1.28 (1.00-1.63)]. There was no significant difference in the frequency of key adverse events, dose reductions or drug discontinuations. None of the biomarkers were prognostic for PFS or OS. Focal adhesion kinase (FAK) overexpression correlated with an OS benefit [HR 2.29 (1.09-4.82)], but not PFS, for CS.

CONCLUSIONS: Saracatinib did not increase the efficacy of a VEGF targeted therapy (cediranib) in this setting. Biomarker analysis did not identify consistent predictive biomarkers.

ClinicalTrials.gov number NCT00942877.

INTRODUCTION

Second line vascular endothelial growth factor (VEGF) targeted therapy is less active than first line VEGF targeted therapy in metastatic clear cell renal cancer (mRCC) [1]. There appears to be significant cross resistance between these drugs rendering subsequent therapy less active than the previous treatment. This has been described as a 'law of diminishing returns' [1, 2].

The mechanism of resistance to VEGF targeted therapy in mRCC is unknown. Alternative pathways such as SRC may play a role in progression of disease [3-5]. Preclinical data shows Src may be involved in stability of the von Hippel-Lindau (VHL) gene and overexpression is associated with poor outcomes in RCC. Further data show that the combination of VEGF targeted therapy and the Src inhibitor, saracatinib, are synergistic in renal cancer cell lines [4]. Therefore, saracatinib may enhance the activity of VEGF targeted therapy. Preclinical work also points towards the potential for a personalised approach with this combination. Overexpression of protein tyrosine phosphatase 1b (PTB1b) and focal adhesion kinase (FAK) appeared to be relevant in determining outcome [4].

Cediranib is a potent VEGF tyrosine kinase inhibitor (TKI) with significant activity in renal cancer patients who have not previously received VEGF targeted therapy, with comparable progression-free survival (PFS) results to those seen with sunitinib, pazopanib and axitinib [1, 6-8]. It was not further developed in mRCC due to established alternatives in this arena. Cediranib was used as it was the only VEGF agent with phase I data in combination with saracatinib. Phase I data showed that cediranib monotherapy was well tolerated and efficacious at a dose of 45mg once daily (OD) [6, 9]. However, a dose reduction for cediranib to 30mg OD was required when used in combination with saracatinib 175mg OD due to a dose-limiting toxicity

(hypertension) [10]. The combination was well tolerated with manageable and largely non-overlapping side effect profiles [10].

Preclinical animal model work suggests PTB1b and FAK may be relevant in predicting response to Src inhibition [4]. It is conceivable that the SRC inhibition is only active in biomarker driven subsets of patients. For this reason a number of relevant biomarkers (SRC, FAK, VHL and hypoxia-inducible factor 2 α (HIF2 α)) were measured from archived tissue.

The aim of this study was to determine if the addition of a SRC inhibitor (saracatinib) to a VEGF TKI (cediranib) led to an improved PFS compared to VEGF inhibition alone in mRCC patients who have already failed VEGF-targeted therapy. We also explored the predictive nature of PTB1b, FAK and other biomarkers in this setting.

MATERIALS AND METHODS

Patient population and study drug

Inclusion criteria included histopathologically-confirmed, measurable (by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1) metastatic clear cell RCC.

Patients were required to have progressive disease on VEGF targeted therapy and be naïve to mammalian Target of Rapamycin (mTOR) inhibitors. Prior immune therapy and >1 line of VEGF targeted therapy was permitted. Adequate end organ function was required. Patients with Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0-2 were permitted. Exclusion criteria focused on the standard exclusion criteria for VEGF targeted therapy studies, such as untreated brain metastases, uncontrolled hypertension/cardiac disease, bleeding, excessive proteinuria and concurrent alternative malignancies.

Patients were randomised (1:1) in a double blinded fashion. They received either cediranib 30mg PO OD + saracatinib 175mg PO OD or cediranib 45mg PO OD + placebo PO OD. Doses were based on single agent and combinations data from phase I-II studies [6, 10]. Dose interruptions (28 days) or reductions were permitted [(i) cediranib 20mg and saracatinib 175mg; (ii) cediranib 15mg and saracatinib 125mg].

Endpoints and assessment.

The primary outcome was to investigate the progression free survival (PFS) of the combination of cediranib and saracatinib compared to cediranib and placebo.

Secondary objectives included response rates (RR), overall survival (OS), adverse events (AEs) and specific biomarker analysis from archived tissue [SRC, VHL, FAK, HIF2 α , PTB1b].

Patients were randomised to receive study drug until progression of disease, death, excess toxicity or discontinuation for another reason. Radiological assessment (RECIST v1.1) occurred eight weekly until progression. No central radiological review occurred. Clinical assessment occurred on a four weekly basis. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 3.0 (CTCAE v3.0). Stratification factors included performance status, duration on first line VEGF targeted therapy (<6 months) and Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic score [11].

Statistical analysis and ethical considerations

The study was designed to detect a 50% improvement (from four months to six months) in median PFS by adding saracatinib to cediranib with 90% power at the 20% 1-sided level of statistical significance. The efficacy was estimated from

previous studies in this area [1, 12]. The primary analysis required 110 PFS events. Approximately 130 patients (65 per arm) were required to achieve this. All analyses were conducted on an intention-to-treat basis. Progression-free survival was compared between the study arms in the context of a Cox model incorporating the baseline stratification factors. The study had appropriate regulatory and ethical approval: ClinicalTrials.gov number NCT00942877.

Biomarker analysis

A tissue microarray (TMA) was constructed from biopsy tissue samples from 78 patients. 4µm thick sections were deparaffinised and rehydrated using xylene and alcohol, and incubated with 0.3% hydrogen peroxide to block endogenous peroxidase activity. Heat-mediated antigen retrieval was performed in citrate buffer (pH 6.0). The following antibodies were used to assess protein expression: VHL (1:200; BD Pharmingen), FAK (1:100; Cell Signalling), SRC (1:200; Cell Signalling), PTB1b (1:2500; Abcam), HIF2α (1:3000, Novus Biologicals). The TMA was then processed using either EnVision Kits (DAKO) or VECTASTAIN ABC Kit (Vector Labs) according to manufacturer's instructions. A single pathologist scored the immunohistochemical (IHC) expression. The immunohistochemical scoring was performed independently and blinded to patient outcome data using the weighted histoscore method. Expression was scored by staining intensity (0, negative; 1+, weakly positive; 2+, moderately positive; 3+, strongly positive), then multiplying with the percentage of tumour cells seen within each section.

RESULTS

Patient population

Between 2010 and 2012, 138 patients were randomised into this study across 16 sites in the UK. Median age for the population was 60 years (interquartile range 54-

67 years). Eighty-two percent of patients previously received sunitinib. Overall 96% received only one previous VEGF targeted therapy, the remainder received two previous lines of VEGF therapy. Twenty percent of patients had previously received immune therapy as initial treatment for metastatic disease prior to subsequent VEGF targeted therapy. Overall 15%, 70%, 15% had MSKCC good, intermediate or poor risk disease respectively at the time of randomisation. The characteristics of the two groups (n=69 for each) were well balanced (Table 1). A consolidated standards of reporting trials (CONSORT) diagram summarises the trial in Figure 1. Sixty-six patients (32%) failed during screening. There were no specific exclusion criteria unique to this study. It was felt that the screen failure rate reflects the advanced nature of the cancer. The presence of brain metastases, worsening performance status and inadequate organ function were common reasons for exclusion.

Efficacy analysis

The median progression free and overall survival for the whole group was 4.1 months (95% confidence interval (CI): 3.1-5.1 months) and 12.0 months (95% CI: 8.5-15.6 months) respectively. Partial responses were seen in 13.0% for cediranib and 14.5% for cediranib and saracatinib respectively ($P>0.05$). Progression of disease as best response occurred 29% for cediranib and 20% for cediranib/saracatinib ($P>0.05$).

There was no significant difference in PFS [5.4 months (3.6-7.3 months) for cediranib and 3.9 (2.4-5.3 months) for cediranib/saracatinib: Hazard Ratio (HR) 1.18 (0.94-1.48) $P>0.05$] or OS [14.2months (11.2-16.8 months) for cediranib and 10.0 (6.72-13.2 months) for cediranib/saracatinib: HR 1.28 (1.00-1.63) $P>0.05$] for the two cohorts (Fig. 2 and Fig. 3). Forest plot analysis showed no consistent subsets that benefited from the combination with the exception of patients with PS 0 (compared to 1 or more) (Fig. 4). Due to the small numbers in this group the results may be artefact. Subsequent targeted therapies (VEGF or mTOR) were given in 25 (36%) cediranib and 33 (47%) cediranib/saracatinib patients.

Adverse events

There were no significant differences in the frequency of key AEs (Table 2). Lethargy and diarrhoea were the most common AEs in both arms (>75% for all grades in both arms and >10% grade 3/4 for both arms). Dose reductions and discontinuation due to AEs with cediranib and cediranib/saracatinib occurred in 13% and 8% vs. 19% and 18% respectively ($P>0.05$). The commonest reason for dose reduction with the combination was diarrhoea (n=4).

Biomarker analysis and exploratory endpoints

Archived tissue was available from 86 (62%) patients. High levels (IHC 2+/3+) of FAK, SRC, PTB1b and HIF2 α were present in 48%, 31%, 38% and 15% respectively. High levels of VHL were seen in 65% of patients. None of these biomarkers were prognostic in terms of PFS or OS (Table 3). FAK expression was predictive of OS [HR: 2.29 (95% CI: 1.09-4.82) $P<0.05$] but not PFS [HR: 0.85 (95% CI: 0.58-2.40) $P>0.05$] (Table 3).

DISCUSSION

The aim of this study was to determine if the addition of a SRC inhibitor (saracatinib) to a VEGF TKI (cediranib) overcame VEGF resistance in patients who progressed after prior VEGF targeted therapy. Preclinical work suggests the combination of cediranib and saracatinib are more active than cediranib alone in mRCC [4]. Our clinical results show this was not the case in VEGF resistant mRCC. Therefore further evaluation of the combination in this setting is not recommended.

The combination was tolerable and comparable in the two study arms. Adverse events were dominated by the toxicity seen with cediranib, with diarrhoea, lethargy,

nausea/vomiting and hand/foot syndrome being most prominent. However 18% of patients discontinued the combination due to toxicity compared to 8% with cediranib alone. This figure (18%) is numerically higher than those seen with axitinib or everolimus in the pivotal trials and may have been relevant in the efficacy results [1, 12]. While indirect comparisons across trials are not valid, the discontinuation rate in this study is high. There are a number of factors which may have contributed to this, ranging from co-morbidities to treatment related toxicity. It underlines the importance of management of toxicity.

Patients' characteristics in the two groups were balanced and in line with previous studies [1, 12]. Most patients had MSKCC intermediate risk disease having failed one line of therapy (96%) (pazopanib or sunitinib in >95%). Forest plot analysis showed the only subgroup of patients which appeared to gain advantage with the combination were those with PS <1. There is no scientific rationale why this may be the case, although previous work with axitinib also suggested PS may be relevant in predicting response to targeted therapy [13].

Cediranib was used as it was the only VEGF agent with phase I data in combination with saracatinib. Had the trial been positive, the correct competitor for the randomised phase III trial would have been axitinib. Pharmacokinetic data from the phase I saracatinib study suggested 175mg OD is an active dose, while 30mg OD of cediranib has activity and was the optimal dose for combinations. This dose of cediranib has resulted in positive studies in other tumours [14, 15]. Overall the doses in this study tested the optimal doses of both arms to best interrogate the efficacy of the combination. However, in our study, it is possible that cediranib at 45mg in the control arm resulted in additional activity compared to 30mg in the combination arm. Nevertheless, these effects are likely to be subtle and it is hard to justify taking either arm forward at this stage. The relatively high discontinuation rate with the

combination (18%) suggests further dose adjustments to improve efficacy are not worthwhile.

The activity of single agent cediranib at 45mg (RR=13% PFS 5.4 months [investigator assessed]) was in line with other agents tested in VEGF refractory disease (axitinib RR=19% PFS 6.5 months [investigator assessed] and sorafenib RR=10% PFS 4.5 months [investigator assessed]) [1]. Cediranib is not being further investigated in mRCC largely due to the competitive landscape. However it has positive results and is being developed in other tumours such as ovarian cancer [14].

The overall survival of 12 months in our trial is modest, especially as most patients were being treated in the second line setting. However, this is within the range of the OS seen in other randomised trials in this setting (14.8 months) [16]. Shorter survival may in part be due to patient selection and limited access to therapies for RCC in the UK, although a significant proportion received further therapy in this study (36-47%). Recent advances with immune therapy showed prolonged survival with nivolumab in VEGF resistant disease [17]. The median overall survival was over 25 months with this agent. This reflects the rapid progress of treatment development in renal cancer.

Preclinical work suggests FAK, which is downstream of SRC, and PTB1b, which is linked to tumour growth in breast cancer, may be important in the identification of patients who benefit from saracatinib and cediranib combination therapy [4, 18]. Our biomarker analysis was unable to confirm this although FAK overexpression predicted survival (but not PFS) to the drug combination. Further exploration of this may be warranted in other settings. It is unclear why FAK was predictive for OS, but not PFS. Given its role in co-ordinating integrin signalling and cell migration, one possibility is that FAK inhibition reduces metastatic spread without affecting local growth of the tumour [19]. Further evaluation is required. It is possible that

biomarker expression from archived tissue was not representative of biomarker expression at the time of randomisation. This questions the validity of this exploratory endpoint. Collection of fresh tissue in randomised trials has proved challenging.

While SRC inhibition may be promising theoretically and preclinically, targeting single tyrosine kinases in VEGF resistant patients may not be optimal due to the tumour heterogeneity seen in clinical setting. To support this, similar results were seen with dovitinib (a FGF-2 inhibitor) in VEGF refractory disease [20]. Other resistance pathways may also be involved (reviewed by [21])

In addition to the limitations discussed above, the lack of independent radiology review to determine PFS is a weakness of this study. Although cediranib is not a licensed treatment in renal cell carcinoma, similarities in the mechanism of action mean that it is uncertain if a different outcome would have been found if axitinib had been used. Therefore, further evaluation in the VEGF resistant setting is not recommended. However, it remains an open question as to whether the combination in a first line setting may be more efficacious by potentially preventing the development of VEGF resistance. Biomarker analysis was carried out on archival tissue. This may have limited the ability to analyse the predictive value of some of the biomarkers in the VEGF resistant setting.

CONCLUSIONS

Together these data suggest that cediranib has activity in this setting, as one might expect in view of its mechanism of action. While direct comparisons with other trials are not possible, indirectly there is nothing from this study to suggest the single agent cediranib would be superior to other agents such as axitinib or everolimus in this setting. The addition of saracatinib to cediranib was relatively well tolerated, but did not improve efficacy. This suggests the preclinical hypothesis is flawed rather than an

inability to give the drugs together. We were also unable to robustly replicate the preclinical biomarker data which pointed towards a personalised approach with these drugs. However, further exploration of FAK may be warranted.

ACKNOWLEDGEMENTS AND FUNDING

This study was funded by Cancer Research UK and AstraZeneca. It was sponsored by CaCTUS – Scottish Clinical Trials Research Unit.

DISCLOSURES

TP has received honoraria and research funding from Novartis, Roche and Pfizer as well as honoraria from Bristol-Myers Squibb.

REFERENCES

1. Rini BI, Escudier B, Tomczak P et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; 378: 1931-1939.
2. Bex A, Haanen J. Tilting the AXIS towards therapeutic limits in renal cancer. *Lancet* 2011; 378: 1898-1900.
3. Chou MT, Anthony J, Bjorge JD, Fujita DJ. The von Hippel-Lindau Tumor Suppressor Protein Is Destabilized by Src: Implications for Tumor Angiogenesis and Progression. *Genes Cancer* 2010; 1: 225-238.
4. Bai L, Yang JC, Ok JH et al. Simultaneous targeting of Src kinase and receptor tyrosine kinase results in synergistic inhibition of renal cell carcinoma proliferation and migration. *Int J Cancer* 2012; 130: 2693-2702.
5. Qayyum T, McArdle PA, Lamb GW et al. Expression and prognostic significance of Src family members in renal clear cell carcinoma. *Br J Cancer* 2012; 107: 856-863.
6. Mulders P, Hawkins R, Nathan P et al. Cediranib monotherapy in patients with advanced renal cell carcinoma: results of a randomised phase II study. *Eur J Cancer* 2012; 48: 527-537.
7. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356: 115-124.
8. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; 28: 1061-1068.
9. Dreys J, Siegert P, Medinger M et al. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. *J Clin Oncol* 2007; 25: 3045-3054.

10. Trarbach T, Schultheis B, Gauler TC et al. Phase I open-label study of cediranib, an oral inhibitor of VEGF signalling, in combination with the oral Src inhibitor saracatinib in patients with advanced solid tumours. *Invest New Drugs* 2012; 30: 1962-1971.
11. Motzer RJ, Mazumdar M, Bacik J et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999; 17: 2530-2540.
12. Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; 372: 449-456.
13. Hutson TE, Lesovoy V, Al-Shukri S et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol* 2013; 14: 1287-1294.
14. Liu JF, Barry WT, Birrer M et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014; 15: 1207-1214.
15. Baselga J, Cervantes A, Martinelli E et al. Phase I safety, pharmacokinetics, and inhibition of SRC activity study of saracatinib in patients with solid tumors. *Clin Cancer Res* 2010; 16: 4876-4883.
16. Motzer RJ, Escudier B, Oudard S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer* 2010; 116: 4256-4265.
17. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *New Engl J Med* 2015; 373: 1803-1813.
18. Bentes-Alj M, Neel BG. Protein-tyrosine phosphatase 1B is required for HER2/Neu-induced breast cancer. *Cancer Res* 2007; 67: 2420-2424.
19. Sulzmaier FJ, Jean C, Schlaepfer DD. FAK in cancer: mechanistic findings and clinical applications. *Nat Rev Cancer* 2014; 14: 598-610.
20. Motzer RJ, Porta C, Vogelzang NJ et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 286-296.
21. Joosten SC, Hamming L, Soetekouw PM et al. Resistance to sunitinib in renal cell carcinoma: From molecular mechanisms to predictive markers and future perspectives. *Biochim Biophys Acta* 2015; 1855: 1-16.

Table 1: Patients' characteristics at baseline

VEGF = vascular endothelial growth factor; MSKCC = Memorial Sloan Kettering Cancer Centre; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2: Most common adverse events (CTCv3.0)**Table 3: Biomarker analysis (prognostic and predictive evaluation)**

*of statistical significance. PFS = progression free survival; OS = overall survival; CI = confidence interval; FAK = focal adhesion kinase; VHL = von Hippel-Lindau; PTB1b = protein tyrosine phosphatase 1b; HIF2 α = hypoxia-inducible factor 2 α .

Figure 1: Consolidated standards of reporting trials (CONSORT) flow diagram

Figure 2: The progression free survival of cediranib and placebo vs. cediranib and saracatinib

Figure 2 legend: Kaplan-Meier analysis for PFS
Cediranib and Saracatinib = 3.9 months (95% CI: 2.4-5.3)
Cediranib and Placebo = 5.4 months (95% CI: 3.6-7.3)
HR = 1.18 (95% CI: 0.94-1.48)

Figure 3: The overall survival of cediranib and placebo vs. cediranib and saracatinib

Figure 3 legend: Kaplan-Meier analysis for OS
Cediranib and Saracatinib = 10.0 months (95% CI: 6.7-13.3)
Cediranib and Placebo = 14.2 months (95% CI: 11.2-17.3)
HR = 1.28 (1.00-1.63)

Figure 4: Forest plot analysis comparing cediranib and placebo vs. cediranib and saracatinib for progression free survival

Figure 4 legend: Forest Plot subset analysis comparing cediranib with cediranib and saracatinib. The dots represent the hazard ratio value and the lines the 95% confidence intervals. LDH = lactate dehydrogenase; CRP = C-reactive protein; MSKCC = Memorial Sloan Kettering Cancer Centre risk score.